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10/521,495	01/13/2005	Gerard O'Beirne	PA0248	2631

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
11/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

melissa.leck@ge.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,495	O'BEIRNE ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-13 and 16-19* is/are pending in the application.

4a) Of the above claim(s) *5 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6, 7, 9-12 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 2, 8, 14, 15 and 20 have been cancelled as filed on 7/6/09.

Claims 1, 3-7, 9-13 and 16-19 are currently pending.

Claims 5 and 13 have been withdrawn.

Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of the following species:

A.) DNA as the "effector nucleic acid";

B.) Fluorescent protein as the "detectable label";

C.) Organic compound as the "modulator";

in the reply filed on 2/6/08 is as previously acknowledged. Accordingly, Claims 5 and 13 are withdrawn due to non-elected species as discussed previously.

Priority

3. This application is filed under 35 U.S.C 371 of PCT/GB03/02983 (filed on 7/10/03).

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers (UK 0216674.2 filed 07/18/02) have been placed of record in the file, as discussed previously.

Specification

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. MPEP 608.01.

Claim Objection(s) / Rejection(s) Withdrawn

6. In light of applicants' amendments to the claims and upon further consideration, the following claim rejection(s) as set forth in the previous office action is(are) withdrawn:

A.) Claims 1-4, 6, 7, 9-12 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

B.) Claims 1-4, 6, 7, 9-12 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

C.) Claims 1-4, 6, 7, 9-12 and 14-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

D.) Claims 1-4, 6, 7, 9-12 and 14-19 are rejected under 35 U.S.C. **103(a)** as being unpatentable over **Thastrup** et al (WO 98/45704; 1998; cited in IDS), in view of **Bastiaens** et al. (WO 00/08054; 2/17/2000; cited previously), and if necessary in view of **Rolls** et al. (Journal of Cell Biology. Vol. 146: 29-43; 7/12/1999) and **Diamond** (WO 00/68661; 11/13/2000; cited in IDS). However, new rejections based on the previously cited references are set forth below due to applicants' amendment to the claims.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Thastrup

10. Claims 1, 3, 4, 6, 7, 9-11 and 16-19 are rejected under 35 U.S.C. **102(b)** as anticipated by or, in the alternative, under 35 U.S.C. **103(a)** as obvious over **Thastrup** et al (WO 98/45704; 1998; cited in IDS). This rejection is necessitated by applicant's amendments to the claims.

The instant claims recite "A method for determining the function of one or more effector nucleic acid sequences from a library of effector nucleic acid sequences comprising:

i) determining the distribution of a detectable label expressed from one of a group of indicator nucleic acid sequences expressed in cells in both the presence and the absence of a group of chemical modulators, which affect said distribution of said detectable label, wherein the cells express one of said effector nucleic acid sequences;

ii) repeat step i) with a different effector nucleic acid sequence from said library of effector nucleic acid sequences;

iii) analyzing the distribution data of said detectable label from all combinations of said effectors, modulator and indicator to derive functional linkages among said effecotrs, modulator and indicator; and

iv) repeating steps i) to iii) with different combinations of effector nucleic acid sequences, chemical modulators and indicator nucleic acid sequences until a function is assigned successfully to said one or more effector nucleic acid sequences."

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells. (e.g. Abstract).

For claim 1: The preamble of the instant claim only recites intended use of the claimed method and does not provide additional structural limitations. See MPEP 2111.02.

Step i): The reference teaches inserting a DNA molecule encoding for a fusion protein comprising "GFP" and another protein (such as a protein kinase) into cells (e.g. Examples; pp.34+), which the GFP encoding DNA reads on the "indicator nucleic acid" as the term is

broadly defined in the instant specification (p.7). The portion of the DNA that encodes for other protein (such as the protein kinase) of the fusion protein read on the "effector nucleic acid sequence" as the term is broadly defined in the instant specification (p.7). The reference also teaches testing the cells in the presence and absence of at least two other molecules including "forskolin" and "norepinephrine" (e.g. p.35, lines 4+), which the "forskolin" or "norepinephrine" reads on "chemical modulator" and as the term "modulator" is broadly defined in the instant specification (p.7).

Step ii): The reference teaches "repeating" the same assay using different effector/indicator constructs having different "effector" such as various kinases PKA, PKC, Erk1, or phosphatases, etc. (e.g. pp.35+; Examples; pp.10+).

Step iii): The reference also teaches detecting the cellular localization of the GFP signals (e.g. p.35, lines 6+), which reads on the "analyzing the distribution of said detectable label" as recited in step iii).

The reference also teaches measuring the "distribution" or localization of the GFP signal in cells before and after addition (or stimulation) of compounds (such as forskolin, norepinephrine, and carbachol) using digital imaging system (e.g. pp.35-36; Figures 3, 7 and 8). The reference teaches comparing the distribution data with stimulation to without stimulation using graphic representations, and digital imaging (e.g. pp.35+).

The reference also teaches analyzing the distribution data and assessing the "stimulatory" effects of either forskolin or norepinephrine (e.g. p.35; Figure 3H). The reference also teaches the function of the protein kinase (i.e. the "effector") by measuring the amount cAMP (e.g. p.35, lines 10+), and thus assigning kinase function of the protein kinase (i.e. detecting "functional

linkage" or assigning function). Therefore, the "functional linkage" among the effector (such as the kinase), modulator (such as forskolin) and the indicator (GFP) can be derived.

Step iv): The reference teaches "repeating" the same assay using different effector/indicator constructs having different "effector" such as various kinases PKA, PKC, Erk1, or phosphatases, etc. (e.g. pp.35+; Examples; pp.10+). The reference also teaches measuring/detecting/analyzing for each of the combinations of components (e.g. pp.35-36; Figures 3, 7 and 8; Examples).

For claim 3: The DNA that encodes for other protein (such as the protein kinase) of the fusion protein read on the "effector nucleic acid sequence" as the term is broadly defined in the instant specification (p.7).

For claim 4: The reference teaches transfecting plasmid containing nucleic acids encoding for a fusion protein (e.g. p.31, lines 1+), which the transfected plasmid (containing double stranded DNA) inherently comprises "an antisense oligonucleotide". An antisense oligonucleotide is the complementary strand of the sense stand (see attached Definition for Antisense downloaded from Merriam-Webster Online Dictionary on 5/8/08). That is any portion (such as a 20 nucleotide portion) of the complementary strand in the plasmid encoding for a protein (such as the protein kinase) read on "an antisense oligonucleotide", because the complementary strand would be "complementary to a segment of genetic material" (i.e. complementary to the sense strand, for example).

For claim 6: The reference teaches expression vectors comprising DNA encoding for the fusion proteins (e.g. pp.30-31).

For claim 7: The reference teaches plasmid expression vectors containing the fusion protein (e.g. pp.30-31).

For claim 8: The reference teaches using GFP (green fluorescent protein) and detecting the fluorescent signals (e.g. pp.36-37), which the GFP reads on a detectable label.

For claim 9: The reference teaches inserting a DNA molecule encoding for a fusion protein comprising "GFP" (reads on the "indicator") and another protein (such as a protein kinase) (reads on the "effector") into cells (e.g. Examples; pp.34+).

For claim 10: The reference teaches using GFP (green fluorescent protein) and detecting the fluorescent signals (e.g. pp.36-37).

For claim 11: The reference teaches using mutant GFP with at least a S65T mutation (e.g. p.30, lines 11+; p.7).

For claim 16: The reference teaches using various cells such as Chinese hamster ovary cells (e.g. p.31, lines 7+), which reads on the eukaryotic cells.

For claim 17: The reference teaches using various cells such as Chinese hamster ovary cells (e.g. p.31, lines 7+) as well as mammalian cells (e.g. pp.5+).

For claim 18: The reference also teaches using cells such as "HUVEC" (human umbilical vein endothelial cells) (e.g. p.22, lines 24+), which reads on the human cells.

For claim 19: The reference teaches using digital imaging system (e.g. pp.35-36; Figures 3, 7 and 8).

Alternatively, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to repeat the same cell based assay with fusion proteins

comprising different proteins (effectors) and modulators. Thastrup et al, teach using commercially available cDNA libraries to generate genes of interest (such as "effector nucleic acid sequences") (e.g. p.14, lines 15+). The reference also teaches generating fusion proteins based on GFP and any gene of interest (e.g. pp.13-14). The Thastrup reference also teaches screening library of compounds (such as a library of "chemical modulators") in cell based assays with GFP fusion proteins (e.g. p.7, lines 15+; p.20, lines 11+). The Thastrup reference explicitly states "contacting or incubating the cell or cells with substances… to exert and influence on the cellular response involving a re-distribution contribution", and the "influence could be substances from a compound drug library". (e.g. p.20, lines 15+).

In addition, it would have been obvious to one skilled in the art to substitute one protein of interest in the fusion protein for the other, or substitute one modulator for the other to achieve the predictable result of "repeating" the same cell based assay with different combination(s) of components (effectors, indicators, etc) as the Thastrup reference teaches the advantages of such screening system. It would have been obvious to one of ordinary skill in the art to apply the standard technique of repeatedly using a reporter based cell system to analyze protein-protein, and protein-chemical interactions in cells as taught by Thastrup, to improve cell based assay and analysis for the predicable result of enabling standard analysis of the functional relationships among proteins and their modulators.

Discussion and Answer to Argument

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert the Thastrup reference "teaches the use of only two components" (Reply, p.11-12).

Applicants specifically argue the GFP fusion protein of the Thastrup reference such as the PKA-GFP fusion "is the equivalent of the indicator in the present invention". Neither the instant specification nor the claims provide any particular structures for the term "indicator" or "effector". In fact, the instant claims recite "fusion" proteins that comprise both the indicator (GFP) and the effector (see claim 9). The instant specification also discloses similar fusion proteins as including both the indicator and the effector (e.g. pp.19+). Thus, it is not clear how the fusion protein (with GFP + another protein) of the instant disclosure would be considered to have both the indicator and the effector, but the same type of fusion protein (with GFP + another protein) would not be considered to have both the indicator and the effector.

Applicants also seem to argue the Thastrup reference does not teach "drug screening methodology" that are not "standard", "function of one" the components is not "known", "networks of functional linkages", etc. (Reply, p.12).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "*drug screening methodology" that are not "standard", "function of one" the components is not*

"known", "networks of functional linkages", etc) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thastrup and Bastiaens

12. Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are rejected under 35 U.S.C. **103(a)** as being unpatentable over **Thastrup** et al (WO 98/45704; 1998; cited in IDS), in view of **Bastiaens** et al. (WO 00/08054; 2/17/2000; cited previously).

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells, as discussed supra. The above rejection over Thastrup is hereby incorporated by reference in its entirety.

Thastrup et al do not explicitly teach the modified GFP has three mutations as recited in **clm 12**.

However, **Bastiaens** et al, throughout the publication, teach various GFP mutants (e.g. Abstract). The reference teaches a GFP mutant (e.g. "YFP5" or "MmGFP5") with mutations including F64L, S65T and S175G (e.g. p.20, Table 1), which read on the GFP mutant as recited in **clm 12**. The reference also teaches the advantages of such GFP mutants including providing a mutant with fluorescent at a unique wavelength (i.e. a red-shifted mutant) (e.g. p.17, lines 1+), longer lifetime, and provides a fluorescent label for multi-labelling experiments (e.g. p.19, lines 5+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use a GFP mutant with the F64L, S65T and S175G mutations for signaling indicator.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a mutant GFP with F64L, S65T and S175G mutations in a screening assay in cells, because Bastiaens et al teaches the advantages of such GFP mutants including providing a mutant with fluorescent at a unique wavelength (i.e. a red-shifted mutant) (e.g. p.17, lines 1+), longer lifetime, and provides a fluorescent label for multi-labelling experiments. Because both of the Thastrup and the Bastiaens references teach methods of expressing GFP mutant proteins, it would have been obvious to one skilled in the art to substitute one GFP mutant for the other to achieve the predictable result of expressing GFP mutants for detecting fluorescent signals.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Thastrup and Bastiaens references have demonstrated the success of using various GFP mutants for cellular screening assays.

Thastrup and Others

13. Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are rejected under 35 U.S.C. **103(a)** as being unpatentable over **Thastrup** et al (WO 98/45704; 1998; cited in IDS), in view of **Bastiaens** et al. (WO 00/08054; 2/17/2000; cited previously), and if necessary, in view of **Gonye** et al. (WO 01/79419; 10/25/01; cited in IDS).

Thastrup et al, throughout the publication, teach methods of using various genetic materials, compounds and cells to assay for molecular functions inside cells, as discussed supra.

Bastiaens et al, throughout the publication, teach various GFP mutants, as discussed supra.

The combination of the Thastrup and Bastiaens teachings as discussed supra is hereby incorporated by reference in its entirety.

Gonye et al, throughout the publication, teach using various reporter fusion protein to provide genomic wide analysis (e.g. Abstract). The reference teaches analyzing genes of the whole genome and comparing data between genomic analysis (e.g. claims). The reference also teaches identifying and determining functions of the genes (e.g. Abstract; claims)

Therefore, it would have been obvious to one of ordinary skill in the art to apply the standard technique of repeatedly using a reporter based cell system to analyze protein-protein, and protein-chemical interactions in cells for genomic wide analysis, to improve cell based assay and analysis for the predicable result of enabling standard analysis of the functional relationships among proteins and their modulators.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Thastrup, Bastiaens and Gonye references have demonstrated the success of using various GFP mutants for cellular screening assays.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Primary Examiner, Art Unit 1639
11/7/09